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### (54) POLYSULFONE SELECTIVE SEPARATION MEMBRANE

#### (57)Abstract:

**PROBLEM TO BE SOLVED:** To control the elution of impurities and to reduce stimuli to living bodies by controlling the content of bioactive glycolipid contained in a membrane as impurities at a regular concentration or below and forming the membrane of a selective separation layer having constant substance permeability on the side of a surface in contact with liquid to be treated.

**SOLUTION:** The content of bioactive glycolipid contained in a membrane as impurities is controlled at 1.3 ppb or below, and the permeability of alubmin by the use of a mixed liquid of water and a solvent selected from N,N-dimethyl acetamide, N,N-dimethyl formamide, N-methyl-2-pyrrolidone, and dimethyl sulfoxide is controlled at 0.5-0.001%. Moreover, a membrane as a selective separation layer having constant substance permeability is formed on the side of a surface in contact with liquid to be treated. In this way, the elution of impurities can be prevented, and stimuli to living bodies can be reduced due to the reduced elution of components from the membrane.

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## CLAIMS

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[Claim(s)]

[Claim 1] The polysulfone system selection demarcation membrane which the bioactive glycolipid content in this film is 1.3 or less ppb, and the permeability of albumin is 0.5 – 0.001% in the film which consists of a hydrophilic giant molecule chosen from either a polysulfone system giant molecule, a polyvinyl pyrrolidone or a polyethylene glycol, and is further characterized by a selection detached core existing in a contact surface side with a processed liquid.

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## DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the polysulfone system selection demarcation membrane used for blood purification, underwater endotoxin removal, etc. in more detail about the selection demarcation membrane aiming at solute removal and purification of a liquid.

[0002]

[Description of the Prior Art] In recent years, many membrane-separation techniques are put in practical use, and in order to separate the specified substance from the mixture of a liquid or a gas or to remove an impurity, various selection demarcation membranes are used. As a material of a selection demarcation membrane, generally the organic system macromolecule is used widely, for example, a polysiloxane, a polyamide, polysulfone, polyolefine, a polyacrylonitrile, polymethacrylate, etc. are mentioned as a cellulose and synthetic macromolecule as naturally-occurring polymers. although the polysulfone system macromolecule is broadly used as an industrial use demarcation membrane especially -- the reason -- chemicals, such as heating, a radiation, and an acid, alkali, -- it is because the resistance which was excellent also to any is shown. Moreover, since it excels also in biocompatibility, recently, it is observed also as a material of a medical-application demarcation membrane, and need is increasing.

[0003] However, since water repellence is the material which cannot be easily damp in water highly, for desired membranous ability and the purpose which especially obtains permeable ability, a polysulfone system macromolecule adds a hydrophilic macromolecule and is produced in many cases. Therefore, when using the film, the hydrophilic macromolecule was eluted or the problem on which a particle and an oligomer component are eluted from a polysulfone system macromolecule was in the processed liquid.

[0004] Many attempts which improve these faults were indicated, for example, at JP,4-300636,A, bridge formation insolubilization of the hydrophilic macromolecule was carried out by irradiating a radiation by the moisture state at the film, it fixed to the film firmly, and

elution is improved. At JP,9-103664,A, by heat-treating the film by dryness, a hydrophilic macromolecule is insolubilized similarly and it is fixing to the film. Moreover, the method of processing the film is also tried of the component which forms a hydrophilic macromolecule and water-insoluble nature complex, and the insolubilization processing which used polyacid, such as polycarboxylic acid and polyphenol, is made in JP,8-32297,B. On the other hand, about the elution of the particle from a polysulfone system macromolecule, or an oligomer component, the resin of a raw material is refined by reprecipitation, or the approach of washing the film with an alcohols solvent is indicated by JP,5-329345,A.

[0005]

[Problem(s) to be Solved by the Invention] However, each Prior art is making an issue of only elution of a hydrophilic macromolecule, a particle, and an oligomer component, and the elution of the other impurity was not taken into consideration. Although the film was generally produced by the wet spinning method, depending on the contamination condition of the water used for coagulation or a washing bath, the impurity of some [ a film production process ] may have mixed the film of a polysulfone system. Moreover, it was also the same as when filling up with water the film which carried out the modularization. In it, the physiological active substance which stimulates a living body is also contained, and it divides, and a glycolipid component has some in which a minute amount also has variegation and powerful bioactive to a living body so that it may be represented by endotoxin. In order to show compatibility with a lipid part high on a polysulfone system macromolecule front face, the film is easy to adsorb, and these are hard to be removed depending on washing. On the other hand, like blood, to the medium with the powerful elution force, compatibility was high, and there was a possibility of it having been eluted and discovering bioactive. Therefore, this invention cancels the trouble of the above-mentioned conventional technique, reduces the elution of the bioactive glycolipid contained in the film as an impurity, and aims at offering the polysulfone system selection demarcation membrane by which stimulative [ to a living body ] was mitigated.

[0006]

[Means for Solving the Problem] In the film which the bioactive glycolipid content contained in the film as an impurity is below fixed concentration, and prepared the selection detached core which has fixed matter permeability in the contact surface side with a processed liquid, the elution of this impurity was stopped and this invention persons found out that stimulative [ to a living body ] was mitigable, as a result of inquiring wholeheartedly, in order to attain said purpose. That is, in the film which consists of a hydrophilic giant molecule chosen from either a polysulfone system giant molecule, a polyvinyl pyrrolidone or a polyethylene glycol, the bioactive glycolipid content in this film is 1.3 or less ppb, and the permeability of albumin is 0.5% - 0.001%, and this invention is a sulfone system selection demarcation membrane further characterized by a selection detached core existing in a contact surface side with a processed liquid.

[0007] It may be the aromatic series polysulfone system macromolecule which has the chemical structure type (1) indicated below to be the polysulfone system macromolecule used by this invention, or the repeat structure of the unit of (2), and you may be the so-called denaturation polysulfone by which the functional group and the alkyl group were added to the ring. Molecular weight does not carry out especially limitation.

-O-Ar-C(CH<sub>3</sub>)<sub>3</sub>-Ar-SO<sub>3</sub>-Ar- (1)

-O-Ar-SO<sub>3</sub>-Ar- (2)

Ar expresses a phenyl group with a ring.

[0008] A hydrophilic giant molecule is chosen from either a polyvinyl pyrrolidone or a polyethylene glycol. A copolymerization object with vinyl system monomers, such as vinyl acetate, may also be included in a polyvinyl pyrrolidone here, and it can be used for it in order to control compatibility with a polysulfone system macromolecule, and the hydrophilic

property on the front face of the film. Although especially such molecular weight is not limited, in order to remain and to make the suitable hydrophilic property for the film give, it is desirable that weight average molecular weight uses at least 100,000 or more things.

[0009] Although various chemical species exist in the glycolipid which has bioactive, the bioactive glycolipid as used in the field of this invention shows the endotoxin of the microorganism origin which mainly exists in process water from a viewpoint of mixing in a wet spinning process. although endotoxin is the dose of dozens ng order in reference and it is known that bioactive is shown in *Homo sapiens* or an animal, if a selection demarcation membrane considers being used as a module which has a predetermined film surface product -- the maximum elution volume from a module -- in other words, the maximum content in a module must be dozens of or less ngs. When the module for blood purification is taken for an example, the film content in a common module is at most 30g, and on the other hand, if the amount which shows bioactive sets weight average as 1 ng/kg to 40kg, it will become 40ng / 30g (1.3ppb) of film. Therefore, the selection demarcation membrane of this invention requires that the content of a bioactive glycolipid should be 1.3 or less ppb. They are 1.0 or less ppb preferably.

[0010] It is thought that the bioactive glycolipid contained as an impurity is eluted from membranous inside and outside and all the front faces in thickness. Moreover, in the separation approach like hemodialysis, the bioactive glycolipid contained in the dialysing fluid which has touched through the film can carry out back flow close to a blood side. In order to make these elution and mixing below into predetermined level, while it has penetrable ability sufficient as film, the permeability to a bioactive glycolipid is a low selection detached core, and it is required for this detached core to exist in a contact surface side with a processed liquid moreover. In addition, the processed liquid as used in the field of this invention shows the thing of the liquid defecated by membrane separation.

[0011] Although the endotoxin as a bioactive glycolipid generally has tens of thousands – millions of molecular weight distributions, in order to cut to the low-molecular-weight field, it makes an index the cow plasma albumin (molecular weight: 67000) which has equivalent molecular weight, and requires that the permeability should be 0.5 – 0.001%. Furthermore, in order to cut elution and to secure a membranous filtration efficiency moreover, it is desirable to make permeability into 0.1 – 0.01%.

[0012] It has the above-mentioned selection detached core in a contact surface side with the liquid used for the selection demarcation membrane of this invention, dissociating, and the other part consists of supporters who do not participate in separation. Supporters have usually taken the sponge-like gestalt. Although it is eluted from all the front faces in the film, since a bioactive glycolipid has the overwhelmingly large rate of the surface area of the supporters who occupy on the whole film, if a selection detached core exists in a contact surface side with a processed liquid, transparency of the effluent to a processed liquid can prevent it as a matter of fact. As a membranous configuration, you may be any of a flat film and a hollow filament.

[0013] Next, as an example of the operation aspect of a polysulfone system selection demarcation membrane which has said description, a polyvinyl pyrrolidone (PVP is called hereafter) is used for a hydrophilic giant molecule, and the case where a film is produced in the shape of a hollow filament is explained to a detail. A film production undiluted solution consists of a polysulfone system macromolecule, PVP, and these common solvents. A solvent can mix and use these at a rate of independent or arbitration, although N and N-dimethylacetamide, N, and N-dimethylformamide, a N-methyl-2-pyrrolidone, and dimethyl sulfoxide are mentioned. Furthermore, water and salts little as an additive may be added in order to control a coagulation rate. Although suitable viscosity is required in order to produce a film in the shape of hollow therefore, a polysulfone system macromolecule is [ 15 – 20 % of

the weight and PVP ] 2 – 8 % of the weight, and the remainder of a desirable presentation is a solvent.

[0014] In order to produce a film in the shape of hollow, when controlling membranous penetrable ability, a presentation is important for a hollow agent. In order to attain the albumin transmission of this invention, it is necessary to use the mixed liquor of water and a solvent, and is chosen from N and N-dimethylacetamide, N, and N-dimethylformamide, a N-methyl-2-pyrrolidone, and dimethyl sulfoxide as a solvent. A solvent is 5 – 40 % of the weight, and the remainder of the desirable presentation of a hollow agent is water. If the permeability of a bioactive glycolipid will become high too much if the rate of a solvent increases more than this, and it becomes low conversely, although permeability will be suppressed, permeable ability sufficient as film cannot be attained. The solvent of the more desirable range is 10 – 25 % of the weight.

[0015] Coincidence is made to breathe out from the duplex spinneret which kept warm an above-mentioned film production undiluted solution and an above-mentioned hollow agent at 30-60 degrees C, and after air transit, if it is made to introduce into the coagulation bath which put in water, the structure of having a selection detached core inside a hollow filament, and having supporters outside will be formed. Thus, after rolling round the solidified hollow fiber to skein and cutting into fixed bundle length, hot water is poured from the cutting plane upper part, and an extant solvent is washed. Before desiccation processing, as an aperture hold-back agent, for example, a glycerol water solution is made to adhere, desiccation processing is performed at 70-80 degrees C for 10 hours or more, and the desiccation film is obtained.

[0016] In case this film is used, it casts to the module which carries out potting of the both ends and has a predetermined film surface product, and sterilization processing is performed if needed. Especially limitation is not carried out that a modularization should just follow a well-known approach. What is necessary is to fill up water with dryness into ethylene OKISAITOGASU, a high pressure steam, radiation irradiation, or a module, and just to process a high pressure steam, radiation irradiation, etc. that what is necessary is just to also choose the sterilization approach from a well-known approach according to an application.

[0017] What is necessary is not to limit especially the method of obtaining the polysulfone system permselective membrane which has the bioactive glycolipid content specified to this invention, but just to choose it from a well-known approach. For example, the approach of using purified water like film production, washing, and a module packer is mentioned, and it is used with one pass after cut-off molecular weight's being 5000 or less and introducing into a hydrophobic ultrafiltration filter the water which passed the column filled up with a polyamine system composition adsorbent or cation exchange resin, without circulating through this filtered water. Moreover, after processing the film obtained as another example, without using purified water with cleaning agents, such as a surfactant and alkali content alcohol, the approach of flushing a cleaning agent with purified water is mentioned. What is necessary is just to use it for independent or arbitration combining these approaches. Since a selection detached core exists inside a hollow filament, the selection demarcation membrane created as mentioned above is used so that a processed liquid may always flow the inside of a hollow filament.

[0018]

[Embodiment of the Invention] Hereafter, although an example explains this invention concretely, this invention is not limited at all by these. In addition, many numeric values used in the example were measured with the following procedures.

(Quantum of the bioactive glycolipid in the film) 20mg of dry film was dissolved by PVP content chloroform 1cc 0.2%, distilled water and diethylether four cc each was added, and fall mixing was carried out. The liquid divided into the bilayer was heated at 70 degrees C after

standing, and evaporation removal of the organic solvent layer was carried out. The quantum of the bioactive glycolipid concentration contained in the obtained water layer was carried out by end SUPESHI (Seikagaku make: ES-50 set), and it \*\*(ed) by film weight, and computed as an endotoxin content in the film.

[0019] (Measurement of albumin transmission) Film surface product 1.5m<sup>2</sup> It connects with the circulator containing 2.5l. (heparinize, protein concentration of 6.5g/deciliter) of cow plasma which warmed the module at 37 degrees C, and a pump is set to both by the side of close [ modular ] and appearance. The pump by the side of module appearance is continuously started circulation by part for 200 cc/of the rates of flow and extracted to a part for 185 cc/in both pumps, and it adjusts so that the filtration rate of flow for 15 cc/may be acquired. It circulates for 60 minutes, returning filtrate to circulation liquid, and circulation liquid and filtrate are extracted in the 60th minute. Laser nephelometer was used for contrast for standard cow albumin, the quantum of the albumin concentration in a sample was carried out, and permeability was computed from the following formula (3).

Transmission (%) =(albumin concentration of albumin concentration / circulation liquid of filtrate) x100 (3)

[0020] (CD11b manifestation trial) Film surface product 0.03m<sup>2</sup> It was filled up with the Homo sapiens fresh blood which contains an anticoagulant in the centrum of a hollow fiber module, and standing contact was carried out for 20 minutes within the 37-degree C incubator. CD11b antibody solution (coal-tar company make: IM0530) 1 \*\* which carried out fluorescent labeling was added to collected restoration blood 5 \*\*, and the cell membrane was fixed to it after the 2-hour reaction using the pretreatment reagent (coal-tar company make: Multi-Q-Prep) at the room temperature. About this specimen, the quantum of the number of CD11b manifestation cells in a granulocyte fraction was carried out with flow cytometer. The rate of the number of CD11b manifestation cells to the number of fixed cells was made into the CD11b incidence rate, and it considered as the stimulative index to a living body.

[0021]

[Example 1] The polysulfone (product made from Amoco— 1700) 18 section and the PVP(BASF [ A.G. ] make: K90, weight average molecular weight 360,000) 5 section were added in the N,N-dimethylacetamide (DMAC is called hereafter) 80 section, the churning dissolution was carried out at 50 degrees C for 8 hours, and the film production undiluted solution was obtained. The hollow agent mixed and prepared the DMAC15 section and the purified water 85 section. Next, it was made to breathe out from the duplex spinneret which kept warm the film production undiluted solution and the hollow agent at 45 degrees C, and after passing the coagulation bath which consists of purified water, it rolled round to skein. After 90-degree C purified water washed the cut bundle, the glycerol water solution was made to adhere 15%, and desiccation processing was carried out at 70 degrees C for 12 hours. It is the obtained film 1.5m of film surface products 2 It cast to the module, it was filled up with purified water, and the gamma ray of 25KG(ies) was irradiated. The bioactive glycolipid content in the obtained film was 0.95ppb, and albumin permeability was 0.05%. The CD11b incidence rate of this film was 8.5%, and stimulative [ to a living body ] was weak.

[0022]

[Example 2] The polysulfone (product made from Amoco— 1700) 18 section and the PVP(BASF [ A.G. ] make: K90, weight average molecular weight 360,000) 5 section were added in the DMAC80 section, the churning dissolution was carried out at 50 degrees C for 8 hours, and the film production undiluted solution was obtained. The hollow agent mixed and prepared the DMAC25 section and the purified water 75 section. Next, it was made to breathe out from the duplex spinneret which kept warm the film production undiluted solution and the hollow agent at 45 degrees C, and after passing the coagulation bath which consists of purified water, it rolled round to skein. After 90-degree C purified water washed the cut

bundle for 2 hours, the glycerol water solution was made to adhere 15%, and desiccation processing was carried out at 70 degrees C for 12 hours. It is the obtained film 1.5m of film surface products 2 It cast to the module, it was filled up with purified water, and the gamma ray of 25KG(ies) was irradiated. The bioactive glycolipid content in the obtained film was 0.65ppb, and albumin permeability was 0.3%. The CD11b incidence rate of this film was 12.5%, and stimulative [ to a living body ] was weak.

[0023]

[Example 3] The polysulfone (product made from Amoco-- 1700) 18 section and the PVP(BASF [ A.G. ] make: K90, weight average molecular weight 360,000) 5 section were added in the DMAC80 section, the churning dissolution was carried out at 50 degrees C for 8 hours, and the film production undiluted solution was obtained. The hollow agent mixed and prepared the DMAC15 section and the non-purified water 85 section. Next, it was made to breathe out from the duplex spinneret which kept warm the film production undiluted solution and the hollow agent at 45 degrees C, and after passing the coagulation bath which consists of non-purified water, it rolled round to skein. After 90-degree C non-purified water washed the cut bundle for 2 hours, the glycerol water solution was made to adhere 15%, and desiccation processing was carried out at 70 degrees C for 12 hours. Purified water washed this film after immersion at 70 degrees C to 95% ethanol of 0.2-N sodium-hydroxide content for 12 hours one whole day and night. The bioactive glycolipid content in the obtained film was 0.35ppb, and albumin permeability was 0.4%. The CD11b incidence rate of this film was 10.5%, and stimulative [ to a living body ] was weak.

[0024]

[The example 1 of a comparison] The polysulfone (product made from Amoco-- 1700) 18 section and the PVP(BASF [ A.G. ] make: K90, weight average molecular weight 360,000) 5 section were added in the DMAC80 section, the churning dissolution was carried out at 50 degrees C for 8 hours, and the film production undiluted solution was obtained. The hollow agent mixed and prepared the DMAC15 section and the non-purified water 85 section. Next, it was made to breathe out from the duplex spinneret which kept warm the film production undiluted solution and the hollow agent at 45 degrees C, and after passing the coagulation bath which consists of non-purified water, it rolled round to skein. After 90-degree C non-purified water washed the cut bundle for 2 hours, the glycerol water solution was made to adhere 15%, and desiccation processing was carried out at 70 degrees C for 12 hours. It is the obtained film 1.5m of film surface products 2 It cast to the module, it was filled up with non-purified water, and the gamma ray of 25KG(ies) was irradiated. The bioactive glycolipid content in the obtained film was 15ppb, and albumin permeability was 0.05%. The CD11b incidence rate of this film was 27.5%, and its stimulus to a living body was high.

[0025]

[The example 2 of a comparison] The polysulfone (product made from Amoco-- 1700) 18 section and the PVP(BASF [ A.G. ] make: K90, weight average molecular weight 360,000) 5 section were added in the DMAC80 section, the churning dissolution was carried out at 50 degrees C for 8 hours, and the film production undiluted solution was obtained. The hollow agent mixed and prepared the DMAC65 section and the purified water 35 section. Next, it was made to breathe out from the duplex spinneret which kept warm the film production undiluted solution and the hollow agent at 35 degrees C, and after passing the coagulation bath which consists of purified water, it rolled round to skein. After 90-degree C purified water washed the cut bundle for 2 hours, the glycerol water solution was made to adhere 15%, and desiccation processing was carried out at 70 degrees C for 12 hours. It is the obtained film 1.5m of film surface products 2 It cast to the module, it was filled up with purified water, and the gamma ray of 25KG(ies) was irradiated. The bioactive glycolipid content in the obtained film was 1.2ppb, and albumin permeability was 2.1%. Where the hollow filament outside of a

small module is filled up with the dialysing fluid created from non-purified water at the time of the CD11b manifestation trial of this film, when it examined, the CD11b incidence rate was 22.0%, and stimulative [ to a living body ] was high.

[0026]

[Effect of the Invention] There are few bioactive glycolipid contents contained in the film as an impurity, since there is also little elution from the film of this component, the stimulus to a living body is mitigated, and the polysulfone system selection demarcation membrane of this invention can be used suitable for fields, such as blood purification.

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(54)【発明の名称】 ポリスルホン系選択分離膜

## (57)【要約】

【課題】 膜中の不純物含量および溶出を少なくして、生体に対する刺激性を軽減したポリスルホン系選択透過膜を提供する。

【解決手段】 ポリスルホン系高分子と親水性高分子とからなる膜で、膜中に含まれる生理活性糖脂質含有率が少なく、かつ、該成分の膜透過の指標としてのアルブミン透過率が低い選択分離層を有し、さらに、該分離層が被処理液との接触面側に存在すると生体に対する刺激性が軽減される。

【効果】 本発明のポリスルホン系選択分離膜は、不純物として膜に含まれる生理活性糖脂質含量が少なく、該成分の膜からの溶出も少ないため、生体に対する刺激が軽減され、血液浄化等の分野に好適に利用できる。

\* ポリスルホン系高分子からの微粒子やオリゴマー成分の溶出については、原料の樹脂を再沈殿で精製したり、膜をアルコール系溶剤で洗浄する方法が特開平5-329345に開示されている。

【0005】

【発明が解決しようとする課題】しかし、従来の技術は、いずれも親水性高分子や微粒子、オリゴマー成分の溶出のみを問題にしており、それ以外の不純物の溶出は考慮されていなかった。ポリスルホン系の膜は、一般に

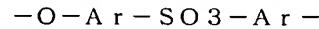
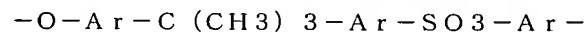
10 湿式紡糸法によって製膜されるが、凝固や洗浄浴に使用する水の汚染状態によっては、製膜過程でいくつかの不純物が混入してくる可能性があった。また、モジュール化した膜に水を充填する場合も同様であった。その中に生体を刺激する生理活性物質も含まれており、とりわけ、糖脂質成分は例えば菌体内毒素に代表されるように、微量でも生体に対して多彩、かつ、強力な生理活性を有するものがある。これらは脂質部分がポリスルホン系高分子表面に高い親和性を示すため膜に吸着されやすく、洗浄によっては除去されにくい。その一方で、血液のように溶出力の強い媒体には親和性が高く、溶出して生理活性を発現するおそれがあった。したがって、本発明は、上記従来技術の問題点を解消し、不純物として膜に含まれる生理活性糖脂質の溶出を減らし、生体に対する刺激性が軽減されたポリスルホン系選択分離膜を提供することを目的とする。

【0006】

【課題を解決するための手段】本発明者らは、前記目的を達成するために銳意検討した結果、不純物として膜に含まれる生理活性糖脂質含量が一定濃度以下で、かつ、

30 被処理液との接触面側に一定の物質透過性を有する選択分離層を設けた膜においては、該不純物の溶出が抑えられ、生体に対する刺激性が軽減できることを見いだした。すなわち、本発明は、ポリスルホン系高分子とポリビニルピロリドン、またはポリエチレングリコールのいずれかから選ばれる親水性高分子とからなる膜において、該膜中の生理活性糖脂質含有率が1.3ppb以下で、かつ、アルブミンの透過率が0.5%~0.001%であり、さらに、被処理液との接触面側に選択分離層が存在することを特徴とするスルホン系選択分離膜である。

【0007】本発明で用いるポリスルホン系高分子とは、下記に示す化学構造式(1)もしくは(2)のユニットの繰り返し構造を有する芳香族ポリスルホン系高分子であり、芳香環に官能基やアルキル基が付加された、いわゆる変性ポリスルホンであってもよい。分子量は特に限定はしない。



(1)

(2)

たはポリエチレングリコールのいずれかから選ばれる。

ここでいうポリビニルピロリドンには、酢酸ビニル等の

【特許請求の範囲】

【請求項1】 ポリスルホン系高分子とポリビニルピロリドン、またはポリエチレングリコールのいずれかから選ばれる親水性高分子とからなる膜において、該膜中の生理活性糖脂質含有率が1.3ppb以下で、かつ、アルブミンの透過率が0.5~0.001%であり、さらに、被処理液との接触面側に選択分離層が存在することを特徴とするポリスルホン系選択分離膜。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は、液体の溶質除去や精製を目的とした選択分離膜に関するもので、さらに詳しくは、血液浄化や水中のエンドトキシン除去等に利用されるポリスルホン系選択分離膜に関するものである。

【0002】

【従来の技術】近年、膜分離技術が数多く実用化されており、液体や気体の混合物から目的物を分離したり、不純物を除去するために様々な選択分離膜が利用されている。選択分離膜の素材としては、一般に有機系高分子が汎用されており、例えば、天然高分子としてセルロース、合成高分子としてはポリシロキサン、ポリアミド、ポリスルホン、ポリオレフィン、ポリアクリロニトリル、ポリメタクリレート等が挙げられる。中でもポリスルホン系高分子は、工業用分離膜として幅広く利用されているが、その理由は、加熱、放射線、および酸・アルカリ等の化学薬品いずれに対しても優れた耐性を示すためである。また、生体適合性にも優れることから、最近では医療用分離膜の素材としても注目され、需要が増加している。

【0003】ところが、ポリスルホン系高分子は撥水性が高く水に濡れにくい素材であるため、所望の膜性能、とりわけ透水性能を得る目的で親水性高分子を添加して製膜されることが多い。そのため、膜を使用する際に被処理液中に親水性高分子が溶出したり、あるいはポリスルホン系高分子から微粒子やオリゴマー成分が溶出する問題があった。

【0004】これらの欠点を改良する試みは数多く開示されており、例えば、特開平4-300636では、含水状態で膜に放射線を照射することで親水性高分子を架橋不溶化させ、膜に強固に固定して溶出を改善している。特開平9-103664では、膜を乾燥状態で熱処理することで、同様に親水性高分子を不溶化し膜に固定している。また、親水性高分子と水不溶性複合体を形成する成分で膜を処理する方法も試みられており、特公平8-32297では、ポリカルボン酸やポリフェノール等の多価酸を用いた不溶化処理がなされている。一方、\*

Arは芳香環でフェニル基を表す。  
【0008】親水性高分子はポリビニルピロリドン、ま

ビニル系モノマーとの共重合物を含んでもよく、ポリスルホン系高分子との親和性や膜表面の親水性をコントロールする目的で使用できる。これらの分子量は特に限定しないが、残存して膜に適当な親水性を付与させるには、重量平均分子量が少なくとも10万以上のものを用いることが好ましい。

【0009】生理活性を有する糖脂質には様々な化学種が存在するが、湿式紡糸工程における混入という観点から、本発明でいう生理活性糖脂質とは、主に工程水に存在する微生物由来の菌体内毒素を示すものである。菌体内毒素は文献的に数十ngオーダーの投与量で、ヒトや動物に生理活性を示すことが知られているが、選択分離膜が所定の膜面積を有するモジュールとして使用されることを考えると、モジュールからの最大溶出量、言い換えれば、モジュール中の最大含有量は数十ng以下でなければならない。血液浄化用のモジュールを例にとると、一般的なモジュール中の膜含有量は多くても30gであり、一方、生理活性を示す量が1ng/kgとして平均的な体重を40kgとすると、40ng/膜30g(1.3ppb)となる。したがって、本発明の選択分離膜は、生理活性糖脂質の含有率が1.3ppb以下であることが必要である。好ましくは1.0ppb以下である。

【0010】不純物として含まれる生理活性糖脂質は、膜の内外および膜厚内のあらゆる表面から溶出してくると考えられる。また、血液透析のような分離方法においては、膜を介して接している透析液に含まれる生理活性糖脂質が血液側に逆流入してくる可能性もありうる。これらの溶出および混入を所定のレベル以下にするためには、膜として充分な透過性能を有する一方、生理活性糖脂質に対する透過率が低い選択分離層であって、しかも、該分離層が被処理液との接触面側に存在することが必要である。なお、本発明でいう被処理液とは、膜分離により清浄化された液のことを示す。

【0011】生理活性糖脂質としての菌体内毒素は、一般に数万～数百万の分子量分布を有しているが、その低分子量領域までカットするには、同等の分子量を有する牛血漿アルブミン(分子量:67000)を指標として、その透過率が0.5～0.001%であることが必要である。さらに、溶出をカットし、しかも、膜の滲過性能を確保するには、透過率を0.1～0.01%とすることが好ましい。

【0012】本発明の選択分離膜は、分離して使用する液との接触面側に上記の選択分離層を有し、それ以外の部分は分離に関与しない支持層からなる。支持層は通常、スポンジ状の形態をとっている。生理活性糖脂質は膜中のあらゆる表面から溶出してくるが、膜全体に占める支持層の表面積の割合が圧倒的に大きいため、被処理液との接触面側に選択分離層が存在すれば、被処理液への溶出物の透過が事実上阻止できる。膜の形状としては

平膜、中空糸のいずれであってもかまわない。

【0013】次に、前記特徴を有するポリスルホン系選択分離膜の実施様態の一例として、親水性高分子にポリビニルピロリドン(以下、PVPと称する)を用い、中空糸状に製膜した場合について詳細に説明する。製膜原液はポリスルホン系高分子、PVP、およびこれらの共通溶剤からなる。溶剤はN,N-ジメチルアセトアミド、N,N-ジメチルホルムアミド、N-メチル-2-ピロリドン、ジメチルスルホキシドが挙げられるが、これらを単独あるいは任意の割合で混合して使用することができる。さらに、凝固速度を制御する目的で、添加剤として少量の水や塩類を加えてもかまわない。中空状に製膜するためには、適切な粘度が必要であるが、そのためには、好ましい組成は、ポリスルホン系高分子が15～20重量%、PVPが2～8重量%であり、残りが溶剤である。

【0014】中空剤は中空状に製膜するためのみでなく、膜の透過性能を制御するうえで組成が重要である。本発明のアルブミン透過率を達成するには、水と溶剤の混合液を用いる必要があり、溶剤としてN,N-ジメチルアセトアミド、N,N-ジメチルホルムアミド、N-メチル-2-ピロリドン、ジメチルスルホキシドから選択される。中空剤の好ましい組成は、溶剤が5～40重量%であり、残りが水である。溶剤の割合がこれ以上高まると、生理活性糖脂質の透過性が高くなりすぎ、逆に低くなると透過性は抑えられるものの、膜として十分な透水性能が達成できない。より好ましい範囲は溶剤が10～25重量%である。

【0015】上述の製膜原液と中空剤とを30～60℃に保温した二重紡糸口金から同時に吐出させ、空中走行の後、水を入れた凝固浴中に導入させると、中空糸の内側に選択分離層、外側に支持層を有する構造が形成される。このように凝固した中空糸膜をカセに巻き取って、一定束長にカットした後、切断面上方から熱水を流して、残存している溶剤を洗浄する。乾燥処理前に孔径保持剤として、例えば、グリセリン水溶液を付着させ、70～80℃で10時間以上乾燥処理を行って乾燥膜を得る。

【0016】該膜を使用する際には、両端をポップティングして所定の膜面積を有するモジュールに成型し、必要に応じて滅菌処理を行う。モジュール化は公知の方法に従えばよく、特に限定はしない。滅菌方法も用途に応じて公知の方法から選択すればよく、例えば、乾燥状態でエチレンオキサイトガス、高圧蒸気、放射線照射、あるいはモジュールに水を充填して高圧蒸気、放射線照射等の処理をすればよい。

【0017】本発明に規定された生理活性糖脂質含有率を有するポリスルホン系選択透過膜を得る方法は特に限定せず、公知の方法から選択すればよい。例えば、製膜、洗浄およびモジュール充填工程で精製水を使用する

方法が挙げられ、ポリアミン系合成吸着剤や陽イオン交換樹脂を充填したカラムを通過した水を、カットオフ分子量が500以下で、かつ、疎水性の限外濾過フィルターに導入後、この濾過水を循環せずにワンパスで使用する。また、別の例としては、精製水を用いずに得られた膜を界面活性剤やアルカリ含有アルコール等の洗浄剤で処理した後、洗浄剤を精製水で洗い流す方法が挙げられる。これらの方法を単独あるいは任意に組み合わせて使用すればよい。以上のように作成された選択分離膜は中空糸の内側に選択分離層が存在するため、常に被処理液が中空糸の内側を流れるように使用する。

#### 【0018】

【発明の実施の形態】以下、実施例により本発明を具体的に説明するが、本発明は、これらにより何ら限定されるものではない。なお、実施例で用いた諸数値は、以下の手順によって測定した。

(膜中の生理活性糖脂質の定量) 乾燥した膜20mgを0.2%PVP含有クロロホルム1ccで溶解し、蒸留\*

$$\text{透過率(%)} = (\text{濾液のアルブミン濃度} / \text{循環液のアルブミン濃度}) \times 100$$

(3)

【0020】(CD11b発現試験) 膜面積0.03m<sup>2</sup>の中空糸モジュールの中空部に、抗凝固剤を含むヒト新鮮血を充填し、37℃のインキュベーター内で20分間静置接触させた。回収した充填血液5容に、蛍光標識したCD11b抗体溶液(コールター社製:IM0530)1容を加えて室温で2時間反応後、前処理試薬(コールター社製:Multi-Q-Prep)を用いて細胞膜を固定した。この検体について、顆粒球画分におけるCD11b発現細胞数をフローサイトメーターによって定量した。一定細胞数に対するCD11b発現細胞数の割合をCD11b発現率とし、生体に対する刺激性の指標とした。

#### 【0021】

【実施例1】ポリスルホン(Amoco社製:P-1700)18部とPVP(BASF社製:K90、重量平均分子量36万)5部をN,N-ジメチルアセトアミド(以下、DMACと称する)80部に添加して50℃で8時間攪拌溶解し、製膜原液を得た。中空剤はDMAC15部と精製水85部とを混合して調製した。次に、製膜原液と中空剤とを45℃に保溫した二重糸口金から吐出させ、精製水からなる凝固浴を通過させた後にカセに巻き取った。切断した束を90℃の精製水で2時間洗浄した後、15%グリセリン水溶液を付着させて70℃で12時間乾燥処理した。得られた膜を膜面積1.5m<sup>2</sup>のモジュールに成型し、精製水を充填して25KGyのγ線を照射した。得られた膜中の生理活性糖脂質含有量は0.95ppbで、かつ、アルブミン透過率は0.05%であった。この膜のCD11b発現率は8.5%であり、生体に対する刺激性が弱かった。

#### 【0022】

\*水およびジエチルエーテル各4ccを加えて転倒混和した。静置後、二層に分離した液を70℃で加熱して、有機溶媒層を蒸発除去した。得られた水層に含まれる生理活性糖脂質濃度をエンドスペーザー(生化学工業社製:ES-50セット)により定量し、膜重量で除して膜中のエンドトキシン含量として算出した。

【0019】(アルブミン透過率の測定) 膜面積1.5m<sup>2</sup>のモジュールを37℃に加温した牛血漿(ヘパリン添加、蛋白濃度6.5g/デシリットル)2.5リットルを含む循環回路に接続し、モジュールの入側、出側の両方にポンプをセットする。両方のポンプを流速200cc/分で循環を開始し、続いてモジュール出側のポンプを185cc/分に絞って、15cc/分の濾過流速が得られるように調整する。濾液を循環液に戻しながら60分間循環し、60分目に循環液と濾液を採取する。サンプル中のアルブミン濃度を、標準牛アルブミンを対照にレーザーネフェロメーターを用いて定量し、下記の式(3)から透過率を算出した。

$$\text{透過率(%)} = (\text{濾液のアルブミン濃度} / \text{循環液のアルブミン濃度}) \times 100$$

(3)

【実施例2】ポリスルホン(Amoco社製:P-1700)18部とPVP(BASF社製:K90、重量平均分子量36万)5部をDMAC80部に添加して50℃で8時間攪拌溶解し、製膜原液を得た。中空剤はDMAC25部と精製水75部とを混合して調製した。次に、製膜原液と中空剤とを45℃に保溫した二重糸口金から吐出させ、精製水からなる凝固浴を通過させた後にカセに巻き取った。切断した束を90℃の精製水で2時間洗浄した後、15%グリセリン水溶液を付着させて70℃で12時間乾燥処理した。得られた膜を膜面積1.5m<sup>2</sup>のモジュールに成型し、精製水を充填して25KGyのγ線を照射した。得られた膜中の生理活性糖脂質含有量は0.65ppbで、かつ、アルブミン透過率は0.3%であった。この膜のCD11b発現率は12.5%であり、生体に対する刺激性が弱かった。

#### 【0023】

【実施例3】ポリスルホン(Amoco社製:P-1700)18部とPVP(BASF社製:K90、重量平均分子量36万)5部をDMAC80部に添加して50℃で8時間攪拌溶解し、製膜原液を得た。中空剤はDMAC15部と非精製水85部とを混合して調製した。次に、製膜原液と中空剤とを45℃に保溫した二重糸口金から吐出させ、非精製水からなる凝固浴を通過させた後にカセに巻き取った。切断した束を90℃の非精製水で2時間洗浄した後、15%グリセリン水溶液を付着させて70℃で12時間乾燥処理した。この膜を0.2N水酸化ナトリウム含有9.5%エタノールに70℃で一昼夜浸漬後、精製水で12時間洗浄した。得られた膜中の生理活性糖脂質含有量は0.35ppbで、かつ、アルブミン透過率は0.4%であった。この膜のCD11b

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発現率は10.5%であり、生体に対する刺激性が弱かった。

【0024】

【比較例1】ポリスルホン (Amoco社製: P-1700) 18部とPVP (BASF社製: K90、重量平均分子量36万) 5部をDMAC 80部に添加して50℃で8時間攪拌溶解し、製膜原液を得た。中空剤はDMAC 15部と非精製水85部とを混合して調製した。次に、製膜原液と中空剤とを45℃に保温した二重紡糸口金から吐出させ、精製水からなる凝固浴を通過させた後にカセに巻き取った。切断した束を90℃の精製水で2時間洗浄した後、15%グリセリン水溶液を付着させて70℃で12時間乾燥処理した。得られた膜を膜面積1.5m<sup>2</sup>のモジュールに成型し、精製水を充填して25KGyのγ線を照射した。得られた膜中の生理活性糖脂質含有量は15ppbで、かつ、アルブミン透過率は0.05%であった。この膜のCD11b発現率は27.5%であり、生体に対する刺激が高かった。

【0025】

【比較例2】ポリスルホン (Amoco社製: P-1700) 18部とPVP (BASF社製: K90、重量平

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均分子量36万) 5部をDMAC 80部に添加して50℃で8時間攪拌溶解し、製膜原液を得た。中空剤はDMAC 65部と精製水35部とを混合して調製した。次に、製膜原液と中空剤とを35℃に保温した二重紡糸口金から吐出させ、精製水からなる凝固浴を通過させた後にカセに巻き取った。切断した束を90℃の精製水で2時間洗浄した後、15%グリセリン水溶液を付着させて70℃で12時間乾燥処理した。得られた膜を膜面積1.5m<sup>2</sup>のモジュールに成型し、精製水を充填して25KGyのγ線を照射した。得られた膜中の生理活性糖脂質含有量は1.2ppbで、かつ、アルブミン透過率は2.1%であった。この膜のCD11b発現試験の際、小型モジュールの中空糸外側に未精製水から作成した透析液を充填した状態で試験を実施したところ、CD11b発現率は22.0%であり、生体に対する刺激性が高かった。

【0026】

【発明の効果】本発明のポリスルホン系選択分離膜は、不純物として膜に含まれる生理活性糖脂質含有量が少なく、該成分の膜からの溶出も少ないため生体に対する刺激が軽減され、血液浄化等の分野に好適に利用できる。

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